



General

Guideline Title

ACR Appropriateness Criteria® follow-up of Hodgkin lymphoma.

Bibliographic Source(s)

Ha CS, Hodgson DC, Advani R, Dabaja BS, Dhakal S, Flowers CR, Hoppe BS, Mendenhall NP, Metzger ML, Plataras JP, Roberts KB, Shapiro R, Smith S, Terezakis SA, Winkfield KM, Younes A, Constone LS, Expert Panel on Radiation Oncology-Hodgkin Lymphoma. ACR Appropriateness Criteria® follow-up of Hodgkin lymphoma [online publication]. Reston (VA): American College of Radiology (ACR); 2014. 16 p. [78 references]

Guideline Status

This is the current release of the guideline.

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Recommendations

Major Recommendations

ACR Appropriateness Criteria®

Clinical Condition: Follow-up of Hodgkin Lymphoma

Variant 1: 22-year-old man with stage IIA supradiaphragmatic Hodgkin lymphoma (ESR 8), treated with ABVD x 4 (PET/CT after 2 cycles) followed by involved-field radiotherapy (IFRT), now 1 month after treatment.

Procedure	Rating	Comments
History and physical examination every 2-4 months for 2 years, then every 6 months for 3 years, then yearly	9	
X-ray chest every 6 months for 2 years, then yearly for 3 years	6	Consider this procedure unless a chest CT is performed.
Rating Scale: 1.2.3 Usually not appropriate; 4.5.6 May be appropriate; 7.8.9 Usually appropriate		

CT chest abdomen and pelvis every 6 months for 2 years, then yearly for 3 years	7	Consider that the frequency of relapse diminishes after 2 years.
FDG-PET/CT whole body every 6 months for 2 years, then yearly for 3 years	2	
FDG-PET/CT whole body at 6 months – if negative then CT chest abdomen and pelvis every 6 months for 2 years, then yearly for 3 years	3	This procedure will likely have a low yield given negative PET/CT after 2 cycles of ABVD.
Laboratory Tests		
CBC 1-2 times per year	7	
Chemistry panel 1-2 times per year	5	
Thyroid panel yearly	8	Consider this test if neck is included in RT field.
ESR 1-2 times per year	5	
Patient Education and Counseling		
Increased long-term risk of second malignancy and cardiac disease	8	
Regular exercise	9	
Healthy diet	9	
Smoking cessation if current smoker	9	
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 2: 28-year-old woman with stage IIBX supradiaphragmatic Hodgkin lymphoma (ESR 30), treated with ABVD x 6 (residual PET avidity after 2 cycles of ABVD, avidity resolved after 6 cycles of ABVD) followed by IFRT, now 1 month after treatment.

Procedure	Rating	Comments
History and physical examination every 2-4 months for 2 years, then every 6 months for 3 years, then yearly	9	
X-ray chest every 6 months for 2 years, then yearly	6	Consider this procedure unless a chest CT is performed.
CT chest abdomen and pelvis every 6 months for 2 years, then yearly for 3 years	8	
FDG-PET/CT whole body every 6 months for 2 years, then yearly for 3 years	2	
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

if negative then CT chest abdomen and pelvis every 6 months for 2 years, then yearly for 3 years	Rating	Comments
Laboratory Tests		
CBC 1-2 times per year	8	
Chemistry panel 1-2 times per year	5	
Thyroid panel yearly	8	Consider this test if neck is included in RT field.
ESR 1-2 times per year	7	
Patient Education and Counseling		
Increased long-term risk of second malignancy and cardiac disease	9	
Monthly self-breast examination	9	
Regular exercise	9	
Healthy diet	9	
Smoking cessation if current smoker	9	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 3: 68-year-old man with stage IA Hodgkin lymphoma with right cervical involvement (ESR 12), treated with ABVD x 4 (PET/CT after 4 cycles) followed by IFRT, now 1 month after treatment.

Procedure	Rating	Comments
History and physical examination every 2-4 months for 2 years, then every 6 months for 3 years, then yearly	9	
X-ray chest every 6 months for 2 years, then yearly	6	Consider this procedure unless a chest CT is performed.
CT neck chest abdomen and pelvis every 6 months for 2 years, then yearly for 3 years	7	
FDG-PET/CT whole body every 6 months for 2 years, then yearly for 3 years	2	
FDG-PET/CT whole body at 6 months – if negative then CT chest abdomen and pelvis every 6 months for 2 years, then yearly for 3 years	3	
Laboratory Tests		

Procedure	Rating	Comments
CBC 1-2 times per year	7	
Chemistry panel 1-2 times per year	5	
Thyroid panel yearly	8	
ESR 1-2 times per year	5	
Patient Education and Counseling		
Increased long-term risk of second malignancy and cardiac disease	8	
Regular exercise	9	
Healthy diet	9	
Smoking cessation if current smoker	9	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 4: 32-year-old woman with history of stage IIA Hodgkin lymphoma with left neck and mediastinal involvement, treated with ABVD x 4 followed by IFRT completing treatment 5 years ago.

Procedure	Rating	Comments
History and physical examination yearly	9	Include thyroid examination and breast examination.
X-ray chest yearly	5	Consider this procedure unless a chest CT is performed.
CT chest abdomen and pelvis yearly	3	
Screening exercise tolerance test and echocardiogram only if symptomatic	6	Screening intervals depend on mediastinal irradiation, adriamycin dose, other risk factors, and findings at the baseline screening.
Screening exercise tolerance test and echocardiogram beginning 5 years after treatment	5	Screening intervals depend on mediastinal irradiation, adriamycin dose, other risk factors, and findings at the baseline screening.
Screening exercise tolerance test and echocardiogram beginning 10 years after treatment	6	Screening intervals depend on mediastinal irradiation, adriamycin dose, other risk factors, and findings at the baseline screening.
Mammography yearly beginning 8-10 years after treatment	8	
Mammography and MRI breast yearly beginning 8-10 years after treatment	7	
CT chest yearly beginning 5 years after treatment	2	Consider this procedure for lung cancer screening.
CT chest yearly beginning 5 years after treatment only if smoker or smoking history	6	
Laboratory Tests		
Rating Scale: 1, 2, 3 Usually not appropriate; 4, 5, 6 May be appropriate; 7, 8, 9 Usually appropriate		

Procedure	Rating	Comments
CBC yearly	5	
Chemistry panel yearly	5	
Thyroid panel yearly	8	
Lipid profile every 1-3 years	8	
Patient Education and Counseling		
Increased long-term risk of second malignancy and cardiac disease	9	
Monthly self-breast examination	7	
Regular exercise	9	
Healthy diet	9	
Smoking cessation if current smoker	9	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 5: 40-year-old man with stage IIIB NS Hodgkin lymphoma involving right neck, mediastinum and para-aortic lymph nodes and ESR of 15 who achieved complete response to ABVD × 6 without radiation therapy per PET/CT, now 3 months after treatment.

Procedure	Rating	Comments
History and physical examination every 2-4 months for 2 years, then every 6 months for 3 years, then yearly	9	
CT neck chest abdomen and pelvis every 6 months for 2 years, then yearly for 3 years	7	
CT neck chest abdomen and pelvis yearly for years 3–5	4	
FDG-PET/CT whole body every 6 months for 2 years, then yearly for 3 years	3	
Laboratory Tests		
CBC 1-2 times per year	1	
Chemistry panel 1-2 times per year	1	
Thyroid panel yearly	1	
ESR 1-2 times per year	3	
Patient Education and Counseling		
Rating Scale: 1 2 3 Usually not appropriate; 4 5 6 May be appropriate; 7 8 9 Usually appropriate		

Procedure	Rating	Comments
Increased long-term risk of second malignancy and cardiac disease		
Regular exercise	9	
Healthy diet	9	
Smoking cessation if current smoker	9	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Summary of Literature Review

Introduction/Background

Routine follow-up evaluation of patients after treatment for Hodgkin lymphoma serves several functions. Detection of relapse is the most important in the first 5 years after treatment. Beyond 5 years, the focus is on monitoring for late effects of therapy. The treatment of Hodgkin lymphoma has evolved greatly over the past few decades and continues to decrease toxicity of treatment while maintaining and improving a high cure rate. With diminishing use of alkylating agents and radiation therapy, the profile of late toxicity, such as second malignancy and radiation-induced organ damage, will continue to improve.

Detection of Relapse

Hodgkin lymphoma remains the main cause of patient death during the first 10 to 15 years of follow-up. Routine follow-up studies are used to detect relapsed disease so that salvage therapy can be instituted in a timely manner.

During the first 5 years of follow-up the focus is placed on disease surveillance, as recurrences are seen most often in this time period. In addition to interim history and physical examination (PE), radiographic tests that have been advocated include chest radiography (CXR), computed tomography (CT), and functional imaging, including position emission tomography (PET). Blood work commonly performed includes complete blood count (CBC), erythrocyte sedimentation rate (ESR), lactate dehydrogenase, and chemistry panel (CHEM).

History and Physical Examination

Interim history appears to be a valuable follow-up tool in detecting relapse of Hodgkin lymphoma. In their review of early-stage Hodgkin lymphoma patients treated at Stanford, a group of researchers found that 55% (59 of 107) of the detected relapses were discovered on the basis of the history, with the most commonly reported symptom being a new lump, followed by constitutional symptoms (fever, night sweats, weight loss) and pain. In a series from Christie Hospital in Manchester, England, a study found that 81% (30 of 37) of relapses were diagnosed in patients who reported symptoms, with the most common symptoms being a new lump, followed by cough, night sweats, and weight loss. One study from Canada found that 45% (10 of 22) of relapses stemmed from patient concerns and 18% (4 of 22) from physician concerns. PE also plays an important role. In the Stanford series, 14% (15 of 107) of the relapses were detected by PE. In the Manchester series, 5% (2 of 37) of relapses were detected by PE. In a multi-institutional pediatric series of 64 relapsed patients, 60% were diagnosed at a routine visit, and patient complaint was the most common initial finding in 47%.

Chest Radiography

CXR is also useful in detecting recurrence of Hodgkin lymphoma, though it assumes a progressively less important role with more common utilization of CT scans of the chest. In the Stanford series, 23% (24 of 107) of relapses were detected by CXR. In the Manchester series, 5% (2 of 37) of relapses were detected by CXR. In the series from Canada, 18% (4 of 22) of relapses were detected by CXR.

Blood Work

Limited data are available on the role of routine blood work in detecting relapses. In the Stanford series, only one relapse was detected by an elevated ESR. CBC, CHEM, and serum copper did not detect any relapse. In the series from Canada, abnormal laboratory findings picked up the same number of relapses as CT scans (2 of 22, 9%) though at a lower cost. No relapse was detected by laboratory abnormality alone in the series by another group of authors.

Computed Tomography

CT scan is routinely included in the follow-up of Hodgkin lymphoma patients. A study from University of Pennsylvania that included 40 patients with relapsed lymphoma (23 were Hodgkin lymphoma), 22 (55%) relapses were detected with surveillance imaging and 18 (45%) were detected by clinical findings. Whether early radiographic detection of asymptomatic relapses has an impact on survival, however, is unknown. A study from Memorial Sloan-Kettering Cancer Center identified 94 patients with relapsed Hodgkin lymphoma and determined that in 36 patients (38%) the relapses were detected by asymptomatic surveillance scans, and in 58 patients (62%) the relapses were diagnosed based on clinical symptoms or findings. The prognostic risk group distribution at relapse was comparable between the two groups. Furthermore, at a median follow-up of 7.4 years, there were no significant differences in 5-year failure-free survival (58.4% vs 59.3%, $P=.9$) and overall survival (62.4% vs 73.3%, $P=0.6$) between patients with asymptomatic relapses detected by surveillance scans and those with clinically evident relapses. This finding was also confirmed in the pediatric series of another study where 36% of relapses were identified by imaging studies with no impact in survival compared to all others. A cost-effectiveness analysis using Markov modeling techniques questioned the cost-effectiveness of annual CT follow-up and showed that with adjustment for quality of life, annual CT in early-stage patients is associated with a decrease in quality-adjusted life expectancy.

A retrospective review of 25 relapsed patients out of 216 who were treated on multicenter Pediatric Oncology Group 9425 trial for Hodgkin lymphoma was performed to study the contribution of surveillance CT compared with clinical findings to detect recurrence. The authors found that 76% of relapses were detected based on symptoms, lab, or PE findings, and only 16% of relapses were detected exclusively by surveillance imaging after the first year. They came to a similar conclusion reached by the previously quoted authors that CT is overused for routine surveillance of patients.

Positron Emission Tomography

Functional imaging studies, in particular PET, are increasingly performed as part of follow-up. Most of the initial studies focused on the effectiveness of post-therapy functional imaging in predicting relapses, showing that PET has a higher specificity than CT in predicting relapses. The superior specificity of PET compared with conventional imaging methods in these studies reflects the ability of PET to detect active disease in abnormal residual masses on CT after treatment. These results suggest that PET may be a useful test for baseline evaluation after first-line therapy and can help identify patients with active residual disease in whom further therapy may be needed. A cost-effectiveness analysis based on 50 patients with unconfirmed complete remission (CRu) or partial response (PR) after first-line therapy showed that the performance of PET in these patients saves costs by limiting the number of patients requiring biopsies, although the comparison may be biased since the assumption was that all patients in CRu/PR will undergo a biopsy if PET is not performed.

Limited data are available for addressing the utility of PET as part of routine follow-up imaging. In the revised response criteria for malignant lymphoma published in 2007, it was stated that there were insufficient data at that time to recommend PET as routine follow-up in lymphoma patients. More recent studies evaluated the use of surveillance PET after an initial negative post-treatment PET, and yielded somewhat conflicting results. One study prospectively followed 421 patients (160 with Hodgkin lymphoma) who had a negative post-treatment baseline PET. Patients underwent PET scans every 6 months for the first 2 years, and then annually after 2 years. In the 160 Hodgkin lymphoma patients, 51 relapses were detected at a mean follow-up of 41 months (41 based on positive PET, 11 inconclusive on PET). Fourteen (27%) of the relapses were missed by CT, and 16 (31%) were missed by clinical signs or symptoms. The findings led the authors to conclude that PET is a valid tool for follow-up of these patients. Of note, in this study, the detected relapses were mostly in the 35 patients with unfavorable disease, defined as having positive PET findings after 2 cycles of chemotherapy. Twenty-six (74%) of these patients relapsed (12, 12 and 2 relapses picked up at the 6-month, 12-month and 18-month scan, respectively), suggesting that PET follow-up may be of greater value in these high-risk patients. In another study in 94 Hodgkin lymphoma patients with negative PET findings after therapy, 155 regular follow-up PET scans were carried out in 67 patients, the timing of which was based on the physician's decision. There were 18 cases of positive PET findings, six of which confirmed malignancies (5 Hodgkin lymphoma relapses and 1 lung cancer). The finding that regular follow-up PET scans correctly identified tumor in only 6 (3.9%) of the 155 PET studies led the authors to conclude that regular follow-up with PET scans in PET-negative patients at the end of therapy is not indicated. However, in patients with clinical findings suspicious for relapse, PET scan may be of value. Another group of researchers came to a similar conclusion. They performed a retrospective review of 211 routine and 88 clinically indicated PET/CT scans for 161 patients status/post at least partial remission on first-line therapy for Hodgkin lymphoma to study the utility of PET/CT in these situations. The positive predictive value (PPV) and false-positive rate of routine PET/CT were 22% and 17%, respectively. PPV and false-positive rate of clinically indicated PET/CT were 37% and 22%, respectively. They concluded that high cost and low PPV make routine PET/CT unsuitable for routine surveillance of patients with Hodgkin lymphoma.

In a combined retrospective analysis from the Massachusetts General Hospital and Dana-Farber Cancer Institute, 192 patients were followed after complete response (CR) to treatment for Hodgkin lymphoma. A total of 474 PET/CT scans and 321 CT scans were performed. The PPV of PET/CT and CT scans for recurrent disease and secondary malignancy were 22.9% and 28.6%, respectively. Their respective false-positive rates were 7.8% and 3.1% ($P=.009$). The cost of detecting a single event was approximately \$100,000. Given the higher false-positive rate of PET scans, the authors have adopted the use of surveillance CT instead of PET/CT to follow patients in first remission from Hodgkin lymphoma.

Investigators from Stanford University reported on their experience with surveillance PET/CT in 113 Hodgkin lymphoma patients after a CR to primary therapy. A total of 326 surveillance PET/CT scans were performed within the first 5 years after treatment. Among the 30 positive scans, 14 were true positives, yielding a positive predictive value of only 47% and an overall recurrence detection rate with PET/CT of 4%. Moreover, 86% of the relapses occurred in the first year. Although 75% of the PET/CT-detected relapses were in asymptomatic patients, the impact of early detection of asymptomatic relapse on salvage outcome is not clear. These data therefore also do not support the routine use of PET/CT surveillance, especially beyond the first year.

In a retrospective review of 134 patients who were followed up after CR or CRu to treatment for Hodgkin lymphoma to study the impact of PET/CT during follow-up, the authors found PET/CT had PPV of 0.98. However, the false-positive rate was not stated. The PPV was very different from that of the Massachusetts General Hospital and Dana-Farber Cancer Institute study, probably due to a different patient population. Not all patients had PET at the end of the first-line treatment in the retrospective review of 134 patients mentioned above, and they probably received referral for PET/CT due to suspected recurrence by treating physicians. The authors recommended PET/CT for certain subgroups of patients such as those with clinical signs of recurrence, those with morphological residual mass within first 24 months, and those with advanced initial stage based on multivariate analysis. (See Variant 1, Variant 2, and Variant 3 above.)

Detection of Second Malignancies

Numerous studies have demonstrated that patients who survive Hodgkin lymphoma are at increased risk for second neoplasms. Solid tumors comprise the majority of cases of second malignancies, with the most common ones being breast cancer and lung cancer. A group of researchers reviewed all trial patients first treated in the British National Lymphoma Investigation and other hospitals to study the long-term risk of second cancer after treatment for Hodgkin lymphoma. The risk of second cancer peaked 5 to 9 years after chemotherapy alone but remained raised beyond 20 to 25 years after combined modality therapy. The risk of treatment-related myelodysplastic syndrome and acute myeloid leukemia has become negligible with diminished use of alkylating agents in the era of ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine).

Breast Cancer

Breast cancers after Hodgkin lymphoma typically occur after a long latency of 10 to 15 years. They are associated with young age at irradiation, and premature menopause has a protective effect. A significant radiation dose-response relationship has been demonstrated, and recent studies also showed a significant relationship between breast cancer risk and radiation field size.

Mammography has been shown to be an effective tool for screening even among these young women. In one study, 81% of 37 women with breast cancer after Hodgkin lymphoma had mammographic abnormalities of a mass and/or microcalcifications. Another group of authors performed a matched cohort study to compare the characteristics and outcomes of breast cancer in women with (253 patients) and without (741 patients) history of radiation therapy for Hodgkin lymphoma and found that breast cancer after radiation therapy for Hodgkin lymphoma was more likely to be detected by screening and at an earlier stage and was more likely bilateral.

Another study prospectively evaluated the utility of mammography in 90 female survivors of Hodgkin lymphoma. During the study period, 10 women developed 12 breast cancers, all of which were evident on mammography. The high frequency of mammographically detected abnormalities supports the value of mammographic screening in these patients. In a study on breast cancer after Hodgkin lymphoma, the authors found that the proportion of patients with early-stage breast cancer was higher in cases that were diagnosed after 1990, which may be due to the more frequent use of mammography screening in the subsequent era.

A study from Princess Margaret Hospital performed annual breast cancer surveillance, mostly with mammography, in 100 female survivors of Hodgkin lymphoma. With 855 person-years of follow-up, 12 cases of breast cancer were diagnosed; 7 presented with palpable mass (4 had negative mammograms in the preceding 6-12 months, 1 had indeterminate mammogram findings, 2 had deferred screening); and 5 were detected by mammogram, 4 of which were ductal carcinoma in situ detected by calcifications. It was noted that 52% of screened women had moderate to extremely dense breast tissue and that these women were more likely to receive adjuvant breast magnetic resonance imaging (MRI).

Similarly in a Stanford study 99 mammograms of female Hodgkin lymphoma survivors were secondarily reviewed, and 60% were noted to have high-density breast tissue, which was also associated with a higher frequency of recall for further imaging.

Breast MRI has been shown to have a higher sensitivity than mammography in genetically predisposed women. However, a recent prospective study performed both screening mammography and breast MRI in 134 women treated with mantle irradiation for Hodgkin lymphoma at age ≤ 35 who were >8 years beyond treatment. This study demonstrated that MRI was not more sensitive than mammograms for breast cancer detection in this patient population. Though the sensitivities of mammography and MRI by themselves were 68% and 67% respectively, combining the 2 modalities brought the sensitivity up to 94%, indicating that the 2 modalities complement each other. Most of the detected breast cancers in this fashion were early stage, which is important given the challenge of treatment in these patients with previous cancer treatment history. The American Cancer Society recommends annual breast MRI as an adjunct to mammogram screening in women who received therapeutic radiation to the chest

at age 30 or younger. Similarly, in the American College of Radiology (ACR) practice guideline for MRI of the breast, one of the indications for MRI screening included a history of mantle irradiation for Hodgkin lymphoma. The National Guideline Clearinghouse (NGC) summary of [ACR Appropriateness Criteria® breast cancer screening](#) also makes recommendations regarding the use of breast MRI in screening.

Lung Cancer

Lung cancer is another well-documented second malignancy after Hodgkin lymphoma. In addition to radiation therapy, prior chemotherapy exposure (alkylating agents in particular) significantly increases the lung cancer risk in a dose-dependent manner. Several studies showed that tobacco use further adds to the risk of lung cancer after Hodgkin lymphoma. In a case-control study, survivors of Hodgkin lymphoma who did not have more than 5 Gy of radiation exposure and had never been exposed to alkylating agents had an 8-fold less risk of lung cancer than survivors who had been treated with radiation therapy and alkylating agents. However, among those with the treatment exposures as well as tobacco exposure, there was a 49-fold increased risk, suggesting a multiplicative interaction between the alkylating agents and/or radiation with tobacco use. Unlike breast cancer, the prognosis of lung cancer after Hodgkin lymphoma is poor, with a median survival of only about 1 year. Given the significantly increased risk of lung cancer after Hodgkin lymphoma, especially among smokers, and the associated poor prognosis, there may be a potential role for screening and early detection of lung cancer in high-risk survivors. Supporting this is a recent publication on the value of low-dose screening CT of the chest for patients at high risk of developing lung cancer. It appears reasonable, based on this finding, to recommend a low-dose screening CT scan for the patients radiated to the chest for Hodgkin lymphoma. However, the ideal interval of screening is not established for these patients. The interval of screening will depend on patients' other risk factors for developing lung cancer such as smoking history and exposure to alkylating agents. A cost-effectiveness analysis suggested that annual low-dose chest CT screening may be a cost-effective strategy among survivors who are smokers.

A retrospective review of 2,567 patients treated for Hodgkin lymphoma (2,335 patients had radiation therapy) in 5 cancer centers/hospitals in The Netherlands found that the risk of mesothelioma was increased by almost 30 fold with radiation therapy compared to the general population, raising the awareness for secondary mesothelioma in this patient population.

Review of a population-based cancer registry from Ontario revealed that surveillance imaging studies rarely lead to salvage therapy, and there was inadequate secondary cancer screening (e.g., colorectal, breast, cervix) for these patients, despite the fact that there are established cancer screening interventions. The authors raise the question that patient and provider education regarding the value of different follow-up tests may improve the quality of follow-up care for these patients.

Detection of Nonmalignant Late Effects of Treatment

Cardiovascular Disease

A number of studies have shown that patients who have been cured of the Hodgkin lymphoma are at significantly increased risk of death from cardiac disease compared with the normal population. A wide spectrum of radiation-induced cardiovascular disease has been identified in asymptomatic survivors of Hodgkin lymphoma, including pericardial disease, coronary artery disease, cardiomyopathy, valvular disease, arrhythmia, and autonomic dysfunction.

The major contributor to the excess risk of cardiac mortality after Hodgkin lymphoma is coronary artery disease, accounting for two-thirds of all cases of fatal cardiac events in survivors of Hodgkin lymphoma. The main risk factor is mediastinal irradiation, and a dose-response relationship has been shown. Presence of other traditional cardiac risk factors further increases the risk of cardiovascular disease after Hodgkin lymphoma. There may be a role for screening for and treatment of modifiable cardiac risk factors. An analysis by a group of authors suggests that lipid screening every 3 years would be the most cost-effective strategy in this population.

The Stanford group prospectively evaluated the role of cardiac screening in asymptomatic Hodgkin lymphoma survivors with history of mediastinal irradiation. A total of 294 patients at a median of 15 years post-treatment were included. In the first publication of the study, the prevalence of valvular abnormalities was found to increase significantly with increasing follow-up time, most of which were rarely picked up by auscultation. Based on the findings, it was estimated that the number of echocardiography screenings needed to identify a candidate for endocarditis prophylaxis decreased dramatically with time following irradiation: 13 for patients at 2 to 10 years, 4 for those at 11 to 20 years, and 1.6 for those more than 20 years, suggesting that echocardiography screening may be beneficial, particularly in those who received their radiation treatment >10 years earlier. However, the optimal screening interval is unclear, and likely needs to be individualized based on treatment-related and host-related cardiac risk factors.

The same group subsequently reported on the high prevalence of diastolic dysfunction based on the screening, with increased incidence for those who are older, for those who have hypertension, diabetes, or wall motion abnormalities, and for those with a longer latency period from radiation treatment to screening. For patients who had completed radiation therapy 11 to 20 years earlier and >20 years earlier, 15% and 23%, respectively, had mild to moderate diastolic dysfunction. Furthermore, the presence of diastolic dysfunction was significantly associated with

increased risk of deaths or events due to coronary artery disease. In the most recent report from the same group, 14% were found to have perfusion defects, impaired wall motion, or both on stress testing. Based on the results, 40 patients (14%) underwent coronary angiography. The angiography showed >50%, <50%, and no stenosis in 55%, 22.5%, and 22.5% of patients, respectively. As a result of the screening, seven of these asymptomatic patients (2.4%) underwent bypass graft surgery. In addition, 23 patients (8%) subsequently developed coronary events during a median of 6.5 years of follow-up, including 10 cases of acute myocardial infarctions. Of note, the median dose to the mediastinum among patients included in this Stanford screening study was 44 Gy (range, 35-54.6 Gy), a dose that is considerably higher than those used in current practice.

In a prospective cardiac screening study, the incidence of asymptomatic cardiac disease in 48 survivors of childhood Hodgkin lymphoma was reported. The median age of the study population at the time of initial therapy was 16.5 years, and the median dose received was 40 Gy. The median follow-up time was 14.3 years. On echocardiogram, 42% were found to have significant valve defects, 75% had conduction defects, and 22% had echocardiographic changes suggestive of restrictive cardiomyopathy. Aortic regurgitation was found to be associated with a decreased physical component score (PCS) on the SF-36 test ($r = -.371$, $P = .011$). A decreased peak myocardial oxygen uptake during exercise ($VO_2\max$), a predictor of mortality in heart failure, was associated with increased fatigue ($r = -.35$, $P = .02$), increased shortness of breath ($r = -.35$, $P = .02$) and decreased PCS ($r = .554$, $P = .00017$). These findings suggest that late effects of treatment can contribute to the increased fatigue level seen in long-term Hodgkin lymphoma survivors. In addition, in survivors with symptoms of fatigue, evaluation for underlying cardiac disease should be considered.

One study performed cardiac MRI in 31 20-year survivors of Hodgkin lymphoma treated with mediastinal radiation therapy (cobalt-60 mainly anterior technique) to assess the potential role of cardiac MRI after mediastinal radiation therapy and found up to 72% of these patients had cardiac pathology. Though these patients were treated with a mainly anterior technique utilizing cobalt-60 to a much higher dose than currently used, the authors raised the potential role of cardiac MRI in following patients after mediastinal radiation therapy for Hodgkin lymphoma.

A group of researchers performed coronary artery calcium (CAC) scoring with CT to correlate with the presence of coronary artery disease in long-term (22 +/- 3 years) survivors (47 patients) of Hodgkin lymphoma after mediastinal radiation therapy. They found CAC score correlated with the presence of coronary artery disease and might be a simple and suitable method to screen for coronary artery disease.

Another group performed a retrospective review of Hodgkin lymphoma patients and their first-degree relatives through the Swedish Cancer Registry to identify stratifying risk factors for surveillance of cardiovascular side effects. The authors found that the risk of cardiovascular disease increased with young age at diagnosis, more than 10 years of follow-up and positive family cardiac history. They also describe a risk-based prospective surveillance strategy under the Swedish Hodgkin Intervention Prevention Study to optimize intervention models for these patients.

Noncoronary atherosclerotic disease has also been identified in long-term Hodgkin lymphoma survivors. In a childhood cancer survivor study, compared to siblings, the relative risk of stroke in Hodgkin lymphoma survivors treated with mantle irradiation was 5.6. However, the absolute excess risk was only 109.8 per 100,000 person-years (or one case per 100 patients followed for 10 years). It was estimated that at least 982 carotid duplex screening ultrasound examinations need to be performed to prevent a stroke, and it is concluded that there was no role for such screening. One study found a significant dose-response relationship for noncoronary atherosclerotic disease in Hodgkin lymphoma survivors. The median doses to the low neck in patients with or without subclavian stenosis were 44 Gy and 36 Gy ($P = .002$), respectively. Smoking and diabetes were also found to be associated with an increased risk of noncoronary atherosclerotic disease. In a cohort study, Hodgkin lymphoma survivors at a median of 17.5 years out from treatment had a 2.2-fold increase in risk of stroke and a 3.1-fold increase in risk of transient ischemic attack compared to the normal population. However, similar to the National Cancer Institute's Childhood Cancer Survivor Study, the absolute excess risk was also low, at 9-12 per 10,000 person-years (0.9-1.2 cases per 100 patients followed for 10 years). Because of its rarity, it was also concluded that screening for carotid disease in this population is not indicated.

Thyroid Abnormalities

Irradiation to the upper mediastinum and low neck can result in thyroid abnormalities. An analysis of patients treated for Hodgkin lymphoma at Stanford demonstrated that the 20-year actuarial risk of thyroid abnormality was 50%, with 90% of the cases being hypothyroidism. Fifty-seven percent of patients with primary hypothyroidism had subclinical disease detected by an elevated serum thyroid-stimulating hormone level with a normal free thyroxine (FT4) level. The greatest risk of hypothyroidism occurred during the first 5 years after treatment, but new cases continued to emerge beyond 20 years after Hodgkin lymphoma. In a study among pediatric Hodgkin lymphoma survivors, risk factors for the development of hypothyroidism included increasing radiation dose, older age at diagnosis, and female gender.

Pneumonitis

Acute radiation pneumonitis occurs in 3% to 10% of patients after mediastinal irradiation. Lung fibrosis as a late effect can result in chronic shortness of breath and contribute to fatigue symptoms in long-term survivors. In the era of combined-modality therapy, the combination of

bleomycin-based chemotherapy with mediastinal irradiation can further potentiate lung toxicity. In a study that prospectively measured the pulmonary function of Hodgkin lymphoma patients during and after bleomycin-based chemotherapy with or without mediastinal radiotherapy, persistently reduced percentage of predicted carbon monoxide diffusing capacity (%DLCO) at 1 year was significantly associated with radiation dose and a smoking history.

Reproductive Function

ABVD, the currently most widely accepted systemic therapy for Hodgkin lymphoma, does not appear to affect gonadal function. However, the newer, more aggressive regimen — bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) for patients with unfavorable or advanced-stage disease — is associated with a significant risk of continued amenorrhea in women and azoospermia in men. In addition, for patients with infradiaphragmatic Hodgkin lymphoma, who comprise 5% to 10% of all early-stage patients, radiation treatment to the pelvis may affect patients' reproductive function. Four to 6 Gy of fractionated radiation therapy to the testes will result in permanent azoospermia in most men. After 8 to 10 Gy of fractionated radiation therapy to the ovaries, most women will develop ovarian failure.

Other Late Effects

Other late effects of Hodgkin lymphoma treatment include immunosuppression, fatigue, psychological distress, and social maladaptation. Awareness of the potential consequences of treatment is necessary for physicians conducting patient follow-up to detect problems at the earliest possible time. (See Variant 4 and Variant 5 above.)

Summary

- The main goals of follow-up studies for Hodgkin lymphoma patients are timely detection of recurrent disease for salvage therapy and monitoring of side effects of the treatment.
- The main focus of follow-up is recurrent disease in the first 5 years, as the majority of relapses occur in this time period. However, the focus shifts to late side effects beyond this time period.
- In general a majority of recurrences can be detected initially by history and physical examination rather than by routine imaging studies or blood tests such as ESR, CBC, and chemistry.
- Though routine surveillance CT scans can detect a proportion of recurrent diseases not detected by history and physical examination, their exact value in terms of life expectancy and cost-effectiveness is unclear. Some investigators believe that surveillance CT scans are currently overused.
- Though PET scan is a useful tool in defining a subset of patients who require additional therapy after completion of the initial therapy, the routine use of PET for surveillance is not recommended in general due to low positive predictive value, high false-positive rate, and unfavorable cost-effectiveness.
- Two of the most common secondary cancers after treatment for Hodgkin lymphoma are breast and lung cancers. Surveillance for these cancers needs to be individualized depending on the risk of their development. The incidence of breast cancer depends on multiple factors such as the age of the patient at treatment and volume and dose of breast radiation. Mammograms and MRI scans of the breasts appear to complement each other in certain high-risk patient populations. The incidence of lung cancers depends on factors such as the use of chemotherapy, alkylating agents in particular, and smoking. There appears to be a role for low-dose screening CT of the chest for patients at high risk for developing lung cancer.
- Some of the nonmalignant long-term sequelae of Hodgkin lymphoma treatment are cardiovascular disease, thyroid abnormalities, pneumonitis, reproductive dysfunction, etc. Follow-up strategies for these sequelae need to be individualized as their risks in general depend on the dose and volume of radiation to these organs, chemotherapy, age at treatment, and predisposing factors for each sequela.

Abbreviations

- ABVD, adriamycin, bleomycin, vinblastine, and dacarbazine
- CBC, complete blood count
- CT, computed tomography
- ESR, erythrocyte sedimentation rate
- FDG, fluorine-18-2-fluoro-2-deoxy-D-glucose
- IFRT, involved-field radiotherapy
- MRI, magnetic resonance imaging
- PET, positron emission tomography
- RT, radiation therapy

Clinical Algorithm(s)

Algorithms were not developed from criteria guidelines.

Scope

Disease/Condition(s)

- Hodgkin lymphoma
- Complications of Hodgkin lymphoma and its treatment, including radiation-induced organ damage and secondary malignancy

Guideline Category

Evaluation

Management

Prevention

Risk Assessment

Screening

Clinical Specialty

Hematology

Internal Medicine

Oncology

Radiation Oncology

Radiology

Intended Users

Health Plans

Hospitals

Managed Care Organizations

Physicians

Utilization Management

Guideline Objective(s)

To evaluate the appropriateness of radiologic and other procedures for the follow-up of patients after treatment for Hodgkin lymphoma

Target Population

Patients with Hodgkin lymphoma who have completed their treatment and response assessment

Interventions and Practices Considered

1. History and physical examination
2. X-ray chest
3. Computed tomography (CT)
 - Chest, abdomen, and pelvis
 - Neck, chest, abdomen, and pelvis
 - Chest
4. Fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET)/CT
 - Whole body
 - Chest, abdomen, and pelvis (if whole body scan is negative at 6 months)
5. Mammography
6. Magnetic resonance imaging (MRI) breast
7. Exercise tolerance test and echocardiogram
8. Laboratory tests
 - Complete blood count (CBC)
 - Erythrocyte sedimentation rate (ESR)
 - Chemistry panel
 - Thyroid panel
 - Lipid profile
9. Patient education and counseling

Major Outcomes Considered

- Utility of radiologic examination in the follow-up of Hodgkin lymphoma
- Positive and negative predictive value of radiologic tests
- Median, failure-free, and overall survival
- Cost-effectiveness of radiologic tests
- Risk of developing relapse of Hodgkin lymphoma, secondary cancers, cardiac disease, stroke, and other complications of treatment

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search Procedure

Staff search in PubMed only for peer reviewed medical literature for routine searches. Any article or guideline may be used by the author in the narrative but those materials may have been identified outside of the routine literature search process.

The Medline literature search is based on keywords provided by the topic author. The two general classes of keywords are those related to the condition (e.g., ankle pain, fever) and those that describe the diagnostic or therapeutic intervention of interest (e.g., mammography, MRI).

The search terms and parameters are manipulated to produce the most relevant, current evidence to address the American College of Radiology Appropriateness Criteria (ACR AC) topic being reviewed or developed. Combining the clinical conditions and diagnostic modalities or therapeutic procedures narrows the search to be relevant to the topic. Exploding the term "diagnostic imaging" captures relevant results for diagnostic topics.

The following criteria/limits are used in the searches.

1. Articles that have abstracts available and are concerned with humans.

2. Restrict the search to the year prior to the last topic update or in some cases the author of the topic may specify which year range to use in the search. For new topics, the year range is restricted to the last 10 years unless the topic author provides other instructions.
3. May restrict the search to Adults only or Pediatrics only.
4. Articles consisting of only summaries or case reports are often excluded from final results.

The search strategy may be revised to improve the output as needed.

Number of Source Documents

The total number of source documents identified as the result of the literature search is not known.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Study Quality Category Definitions

Category 1 - The study is well-designed and accounts for common biases.

Category 2 - The study is moderately well-designed and accounts for most common biases.

Category 3 - There are important study design limitations.

Category 4 - The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:

- a. The study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description).
- b. The study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence.
- c. The study is an expert opinion or consensus document.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The topic author drafts or revises the narrative text summarizing the evidence found in the literature. American College of Radiology (ACR) staff draft an evidence table based on the analysis of the selected literature. These tables rate the strength of the evidence (study quality) for each article included in the narrative text.

The expert panel reviews the narrative text, evidence table, and the supporting literature for each of the topic-variant combinations and assigns an appropriateness rating for each procedure listed in the table. Each individual panel member assigns a rating based on his/her interpretation of the available evidence.

More information about the evidence table development process can be found in the ACR Appropriateness Criteria® Evidence Table Development document (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

Description of Methods Used to Formulate the Recommendations

Rating Appropriateness

The appropriateness ratings for each of the procedures included in the Appropriateness Criteria topics are determined using a modified Delphi methodology. A series of surveys are conducted to elicit each panelist's expert interpretation of the evidence, based on the available data, regarding the appropriateness of an imaging or therapeutic procedure for a specific clinical scenario. American College of Radiology (ACR) staff distribute surveys to the panelists along with the evidence table and narrative. Each panelist interprets the available evidence and rates each procedure. The surveys are completed by panelists without consulting other panelists. The appropriateness rating scale is an ordinal scale that uses integers from 1 to 9 grouped into three categories: 1, 2, or 3 are in the category "usually not appropriate"; 4, 5, or 6 are in the category "may be appropriate"; and 7, 8, or 9 are in the category "usually appropriate." Each panel member assigns one rating for each procedure for a clinical scenario. The ratings assigned by each panel member are presented in a table displaying the frequency distribution of the ratings without identifying which members provided any particular rating.

If consensus is reached, the median rating is assigned as the panel's final recommendation/rating. Consensus is defined as eighty percent (80%) agreement within a rating category. A maximum of three rounds may be conducted to reach consensus. Consensus among the panel members must be achieved to determine the final rating for each procedure.

If consensus is not reached, the panel is convened by conference call. The strengths and weaknesses of each imaging procedure that has not reached consensus are discussed and a final rating is proposed. If the panelists on the call agree, the rating is proposed as the panel's consensus. The document is circulated to all the panelists to make the final determination. If consensus cannot be reached on the call or when the document is circulated, "No consensus" appears in the rating column and the reasons for this decision are added to the comment sections.

This modified Delphi method enables each panelist to express individual interpretations of the evidence and his or her expert opinion without excessive influence from fellow panelists in a simple, standardized and economical process. A more detailed explanation of the complete process can be found in additional methodology documents found on the [ACR Web site](#) (see also the "Availability of Companion Documents" field).

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

- A cost-effectiveness analysis using Markov modeling techniques questioned the cost-effectiveness of annual computed tomography (CT) follow-up and showed that with adjustment for quality of life, annual CT in early-stage patients is associated with a decrease in quality-adjusted life expectancy.
- A cost-effectiveness analysis based on 50 patients with unconfirmed complete remission (CRu) or partial response (PR) after first-line therapy showed that the performance of positron emission tomography (PET) in these patients saves costs by limiting the number of patients requiring biopsies, although the comparison may be biased since the assumption was that all patients in CRu/PR will undergo a biopsy if PET is not performed.
- A cost-effectiveness analysis suggested that annual low-dose chest CT screening may be a cost-effective strategy among survivors who are smokers.
- Presence of traditional cardiac risk factors further increases the risk of cardiovascular disease after Hodgkin lymphoma. One analysis suggests that lipid screening every 3 years would be the most cost-effective strategy in this population.
- In a combined retrospective analysis from the Massachusetts General Hospital and Dana-Farber Cancer Institute, 192 patients were followed after complete response (CR) to treatment for Hodgkin lymphoma. A total of 474 PET/CT scans and 321 CT scans were performed. The positive predictive value (PPV) of PET/CT and CT scans for recurrent disease and secondary malignancy were 22.9% and 28.6%, respectively. Their respective false-positive rates were 7.8% and 3.1% ($P=.009$). The cost of detecting a single event was approximately \$100,000. Given the higher false-positive rate of PET scans, they have adopted the use of surveillance CT instead of

PET/CT to follow patients in first remission from Hodgkin lymphoma.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Criteria developed by the Expert Panels are reviewed by the American College of Radiology (ACR) Committee on Appropriateness Criteria.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are based on analysis of the current literature and expert panel consensus.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Selection of appropriate radiologic imaging procedures for follow-up of patients with Hodgkin lymphoma
- Timely detection of recurrent disease for salvage therapy

Potential Harms

False-positive findings of diagnostic tests

Qualifying Statements

Qualifying Statements

The American College of Radiology (ACR) Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists, and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the U.S. Food and Drug Administration (FDA) have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Ha CS, Hodgson DC, Advani R, Dabaja BS, Dhakal S, Flowers CR, Hoppe BS, Mendenhall NP, Metzger ML, Plataras JP, Roberts KB, Shapiro R, Smith S, Terezakis SA, Winkfield KM, Younes A, Constine LS, Expert Panel on Radiation Oncology-Hodgkin Lymphoma. ACR Appropriateness Criteria® follow-up of Hodgkin lymphoma [online publication]. Reston (VA): American College of Radiology (ACR); 2014. 16 p. [78 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

1999 (revised 2014)

Guideline Developer(s)

American College of Radiology - Medical Specialty Society

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Guideline Committee

Committee on Appropriateness Criteria, Expert Panel on Radiation Oncology--Hodgkin Lymphoma

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Financial Disclosures/Conflicts of Interest

Not stated

Guideline Status

This is the current release of the guideline.

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Guideline Availability

Electronic copies: Available from the [American College of Radiology \(ACR\) Web site](#) .

Print copies: Available from the American College of Radiology, 1891 Preston White Drive, Reston, VA 20191. Telephone: (703) 648-8900.

Availability of Companion Documents

The following are available:

- ACR Appropriateness Criteria®. Overview. Reston (VA): American College of Radiology; 2013 Nov. 3 p. Electronic copies: Available from the [American College of Radiology \(ACR\) Web site](#) .
- ACR Appropriateness Criteria®. Literature search process. Reston (VA): American College of Radiology; 2013 Apr. 1 p. Electronic copies: Available from the [ACR Web site](#) .
- ACR Appropriateness Criteria®. Evidence table development – diagnostic studies. Reston (VA): American College of Radiology; 2013 Nov. 3 p. Electronic copies: Available from the [ACR Web site](#) .
- ACR Appropriateness Criteria®. Evidence table development – therapeutic studies. Reston (VA): American College of Radiology; 2013 Nov. 4 p. Electronic copies: Available from the [ACR Web site](#) .
- ACR Appropriateness Criteria® follow-up of Hodgkin lymphoma. Evidence table. Reston (VA): American College of Radiology; 2014. 34 p. Electronic copies: Available from the [ACR Web site](#) .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on December 15, 2005. The updated information was verified by the guideline developer on January 19, 2006. This NGC summary was updated by ECRI Institute on December 23, 2010 and August 27, 2014.

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